INTRODUCTION

The purpose of this meeting is: 1) to update to the Antivirals Advisory Committee on the data supporting the safety and efficacy of Peg-Intron and Rebetol for the treatment of adult patients with chronic hepatitis C infection and 2) to discuss questions about dosing at the time of approval that resulted in the requested postmarketing studies.

Filing of application

On February 5, 2001, Schering Corporation submitted to the Center for Biologics Evaluation and Research a Biologics License Application Supplement (BLAs) for PEG-Intron™ (peginterferon alfa-2b, SCH 54031) and REBETOL™ (ribavirin, USP; SCH 18908) combination therapy for the treatment of chronic hepatitis C.

Study products

Peg-interferon alfa-2b is manufactured by conjugation of interferon alfa-2b with a 12-KD monomethoxy polyethylene glycol molecule. The clearance of peginterferon alpha is longer than that of interferon allowing once weekly dosing and increased drug exposure compared to interferon alpha. Ribavirin is a guanosine analogue that has *in vitro* antiviral activity against a number of different RNA viruses. Ribavirin enters the red blood cell and has an intracellular half-life of approximately 300 days. The major efficacy trial in the BLAs was a 3 arm trial in which patients were randomized to one of two different regimens of peginterferon alfa-2b with ribavirin or to Rebetron.

Chronic hepatitis C

HCV causes 20% of all cases of acute viral hepatitis and 70-90% of all cases of chronic viral hepatitis. The acute infection is asymptomatic in the majority of cases. Spontaneous recovery from infection occurs in 15% of cases. Patients with chronic HCV infection have persistent viremia and in most cases abnormal ALT levels.

In the US around 50% of children and 85% of adults infected with HCV develop chronic hepatitis; approximately 4 million persons are chronically infected with HCV. After decades, liver cirrhosis develops in about 20% of adults with chronic HCV infection. In children with chronic HCV the incidence of cirrhosis is lower compared to adults due to shorter duration of infection and possibly slower rate of progression of disease. The development of cirrhosis is associated with liver failure, with portal hypertension and their related complications, and with the development of hepatocellular carcinoma. Chronic HCV infection causes 12,000 deaths per year and is the primary cause for liver transplantation in the US. Genotype 1 is the most common (70%) HCV genotype and is less likely to respond to treatment compared to HCV genotypes 2 and 3. High circulating HCV load, defined as $>2 \times 10^6$ RNA copies/ml serum, and presence of liver cirrhosis are two other indicators of unfavorable response to treatment.

Treatment of chronic hepatitis C

Alpha interferons were the first antiviral agents to be licensed for the treatment of patients with chronic hepatitis C. Alpha interferons induce loss of detection of circulating HCV RNA, normalization of serum transaminase levels, and modest reduction in liver inflammation. At 6 months after the end of alpha interferon monotherapy the proportion of patients with undetectable HCV RNA is low (<20%). Combination treatment with alpha interferon and ribavirin roughly doubles (to around 40%) the proportion of responders and is the most efficacious therapy currently available for chronic hepatitis C.

Peginterferon alfa-2b has been shown to be more efficacious than interferon alfa-2b. In a randomized trial comparing 3 doses of peginterferon alfa-2b monotherapy (0.5, 1,and 1.5 yg/kg) to interferon alfa-2b monotherapy, the two higher doses of peginterferon alfa-2b resulted in sustained response rates that were roughly twice as high as with Intron A. The severity and incidence of peginterferon alfa-2b -induced toxicity appears to be higher than the toxicity induced by interferon alfa-2b. Although no direct, head to head studies have compared peginterferon alfa-2b with Rebetron (combination of Intron A and Rebetol), an assessment of treatment responses across different studies suggests that peginterferon alfa-2b alone is likely to be less effective than combination therapy with interferon alpha and ribavirin.

Arguably the risk/benefit of interferon alfa monotherapy for chronic HCV is no longer acceptable particularly for patients with poor prognostic indicators (e.g. HCV genotype 1 and high viral titers). The rate of response to interferon monotherapy is very low in these patients.

There is no definitive evidence that loss of detection of HCV RNA six months after the end of treatment (the primary outcome measure of most studies) will decrease the incidence of serious long-term outcomes, including progression of liver disease to cirrhosis and its associated complications including hepatocellular carcinoma.

Alpha interferons adversely affect a number of organ systems and may induce a number of serious toxicities, including neuropsychiatric disorders, autoimmune disorders, ischemic disorders, and disorders of host defenses. The majority of patients on alpha interferons experience fatigue and flu-like symptoms; alpha interferons also commonly induce nausea, vomiting, anorexia and weight loss. They may induce liver decompensation in patients with chronic liver failure. Interferons are abortifacients.

Toxic effects of ribavirin include hemolytic anemia, teratogenicity, embryocidal activity, and mutagenesis. The main dose-limiting toxicity of ribavirin is hemolytic anemia, which, if severe, may induce ischemic cardiac or neurologic events. The anemia is usually reversible once treatment is discontinued.

LISTING OF CLINICAL STUDIES

The table below lists the clinical studies that support this license application.

Table 1. Studies of Peginterferon α-2b plus Ribavirin in Patients with Chronic Hepatitis C

Study No. Subject No.	Study Design	Study Drug Doses
[redacted] N= 72	Phase 1, open-label, active-control, Parallel group, multiple-dose, study.	Peginterferon α-2b (0.35-1.4 µg/kg SC QW) plus Ribavirin (600-1000/1200 mg PO) for 24 weeks

——— N= 1530	Phase 3 multicenter, randomized, open-label, active-control, parallel group study with 48 weeks of treatment and 24 weeks of follow-up.	Peginterferon α-2b (1.5 µg/kg SC QW) plus Ribavirin (800 mg/day PO). Peginterferon α-2b (1.5 µg/kg SC QW for 4WK then 0.5 µg/kg for 44 WK) plus Ribavirin (1000-1200 mg/day PO). Interferon α-2b A $3x10^6$ U SC TIW plus Ribavirin 1000-1200 mg/day PO.

PROTOCOL ' ———

HYPOTHESES, DOSE SELECTION

The phase 3 study was a single multinational study run under two designations, ——— for US sites, and ' ——— international sites. Data from all study sites were combined for a single analysis.

Study hypotheses and rationale for dose selection

The sponsor used the following data to select the doses to be studied.

Peginterferon

A dose ranging study (Protocol ———, of peginterferon monotherapy (0.5, 1, or 1.5 µg/kg SC once weekly) versus interferon monotherapy (3 x 10^6 U SC three times weekly) in patients with chronic HCV hepatitis was ongoing. As shown in the table below an analysis of antiviral activity after 6 months of treatment showed that the proportion of patients with undetectable HCV-RNA was numerically higher in all three peginterferon groups compared to interferon alpha 2 b (Intron-A). The proportion of responders was highest in the 1.5 µg/kg dose group (see **Table 2**).

Table 2. Antiviral Activity (HCV RNA <2,000 copies/ml) at 24 Weeks of Treatment

Treatment Groups[1]			
PEG 0.5 µg/kg N=315	**PEG 1.0 µg/kg N=297**	**PEG 1.5 µg/kg N=304**	**IFN 3 x 10^6 U N=303**
42%	48%	57%	32%

[1]Protocol ' ———

Based on the degree of anti-viral activity achieved with peginterferon alfa-2b monotherapy, it was believed that treatment with peginterferon alfa-2b and ribavirin might be more efficacious compared to treatment with interferon alfa-2b plus ribavirin. The results also suggested to the sponsor that the 1.5 µg/kg dose might be superior to the 1.0 µg/kg dose. Unfortunately, after study ——— was completed the data showed that the efficacy of the peginterferon 1.5 µg/kg dose was not superior to that of the peginterferon 1.0 µg/kg dose (23% response vs. 24%). The incidence of adverse events was somewhat higher in the peg 1.5 dose group compared to the peg 1.0 dose group. As a result of more favorable risk benefit the agency licensed the peginterferon 1.0 µg/kg dose for monotherapy of HCV. At the time of licensure of peginterferon monotherapy, the combination study was well underway. Thus, no studies were available evaluating peginterferon 1.0ug/kg in combination with ribavirin.

Peginterferon and ribavirin

A phase 1 study (protocol ———— evaluated the following peginterferon plus ribavirin combination treatments in 72 patients with chronic hepatitis C infection:
-Peginterferon 0.35 μg/kg/week plus ribavirin 600 or 800 mg/day
-Peginterferon 0.7 μg/kg/week plus ribavirin 600, 800, or 1000-1200 mg/day
-Peginterferon 1.4 μg/kg/week plus ribavirin 600, 800, or 1000-1200 mg/day

The following observations were made: The peginterferon 0.35 μg/kg dose appeared to have antiviral activity only when combined with ribavirin 800 mg. The peginterferon 0.7 μg/kg dose appeared to be most active when combined with ribavirin 1000-1200 mg. The peginterferon 1.4 μg/kg dose appeared to be equally active with the three ribavirin doses tested.

Rationale for dose selection

Based on the preliminary results of the two studies discussed above, the sponsor hypothesized that peginterferon 1.5 μg/kg once weekly plus ribavirin 800 mg daily would be superior in efficacy and would have a more favorable safety profile than the licensed regimen of Interferon $3x10^6$ Units thrice weekly plus ribavirin 1000-1200 mg daily. The sponsor also hypothesized that peginterferon 0.5 μg/kg once weekly plus ribavirin 1000-1200 mg daily would be similar in efficacy and would have a more favorable safety profile than the IFN/R. The final hypothesis was that an induction treatment with peginterferon 1.5 μg/kg once weekly for 4 weeks would boost the response to treatment in the PEG 0.5/R arm.

Thus, the selection of the peginterferon and ribavirin doses to be tested in the present efficacy study (————), was based on preliminary in-treatment data on peginterferon monotherapy which was not borne out by the end-of-study results, and on a small dose-ranging study of peginterferon and ribavirin in combination.

SUMMARY OF THE EFFICACY TRIAL (————)

Study design

Multi-center, randomized, open-label, active-controlled (INTRON A/REBETOL), parallel group, phase 3 study of two PEG-Intron/REBETOL regimens in approximately 1500 subjects with chronic hepatitis C. Subjects were randomly assigned to three treatment arms (1:1:1) with stratification based on HCV genotype (1 vs. non-1) and presence of liver cirrhosis. Subjects were treated for 48 weeks and were followed up for 24 weeks post-treatment.

Dosing

The comparator arm was REBETRON at the labeled dosing regimen of interferon alfa-2b $3x10^6$ Units administered subcutaneously three times weekly together with ribavirin 1000-1200 mg/day administered orally for 48 weeks.
The experimental treatment groups received one of the following two regimens:

1. Peginterferon 0.5 μg/kg SC once weekly plus ribavirin 1000/1200 mg/day orally in 2 divided doses for 44 weeks. This regimen was preceded by a 4-week induction period with peginterferon 1.5 μg/kg/week plus ribavirin 1000/1200 mg/day. The

induction treatment was used in the belief that it would induce more rapid loss of HCV-RNA.

2. Peginterferon 1.5 µg/kg SC once weekly plus ribavirin 800 mg/day orally in 2 divided doses for 48 weeks. The 800 mg dose of ribavirin was intended to minimize the risk of additive/synergistic hematologic toxicity of interferon and ribavirin.

Dose modification rules

Patients who reduced their ribavirin dose because of adverse events continued on the same reduced dose of ribavirin (600 mg daily divided as 200 mg in am and 400 mg in pm) even after the adverse event resolved. Patients who reduced their dose of peginterferon or interferon (doses were halved in all treatment groups) because of adverse events resumed full dosing when the adverse event resolved. If the adverse event recurred the subject could return to the previously tolerated lower dose level for the remainder of the study. Alternatively the subject could permanently discontinue treatment.

Patients who interrupted treatment for longer than two weeks terminated treatment permanently and entered the follow up period. Subjects were to be withdrawn from study treatment for the following reasons: Serious or life-threatening (grade 4) adverse event, pregnancy, subject's or investigator's choice, non-compliance, failure to disclose history of suicide ideation or attempt.

Specific rules were used for development of depression, abnormal hemoglobin, neutrophil and platelet counts, bilirubin, creatinine, and transaminase levels.

Inclusion criteria

Study subjects had to meet the following criteria.
Adult men and women 18-70 years of age. Subjects > 65 years must be in good health. Serum positive for HCV-RNA by quantitative PCR assay. Elevated ALT. Liver biopsy within 12 months with diagnosis of chronic hepatitis. Compensated liver disease. Laboratory criteria: Hgb >12 g/dL in women, >13 g/dL in men; WBC >3,000/mm^3, ANC >1,500/mm^3 platelets >100,000/mm^3; direct and indirect bilirubin, albumin, TSH, serum creatinine, WNL; ANA<1:160; HIV and HBsAg negative; alpha fetoprotein WNL, or if $\leq$50 ng/ml a negative abdominal ultrasound; serum pregnancy test negative. Practicing adequate contraception.

Exclusion criteria

Subjects were to be excluded from enrollment into the study for the following reasons. Previous treatment with any interferon; treatment with any other antiviral or immunomodulatory agent within 2 years. Hypersensitivity to interferon, peginterferon or ribavirin. Any other cause for liver disease other than chronic HCV. Hemophilia or any other condition that would prevent a liver biopsy. Hemoglobinopathies, advanced liver disease, organ transplants. Certain pre-specified preexisting medical conditions

Efficacy outcomes

Primary: The primary efficacy outcome was loss of detectable serum HCV-RNA measured by quantitative polymerase chain reaction. A subject was classified as a responder if the subject was HCV-RNA negative at 24 weeks post-treatment. All other subjects, including those who discontinued before the final HCV-RNA evaluations were obtained, were considered non-responders.

Secondary: The following were the principal secondary endpoints listed in order of importance.

1. Normalization of ALT at 24 wks post-treatment.
2. Loss of HCV-RNA detection at the end of treatment.
3. Normalization of ALT at the end of treatment.
4. Improvement from baseline in biopsy scores (Knodell and Metavir) at 24 wks post-treatment. The changes in the qualitative scores that define improvement in liver biopsy are very small. It is not clear how clinically meaningful such changes are.
5. Health Related Quality of Life (HQL) was evaluated using the SF-36 scale with additional generic scales and hepatitis C specific scales.

Clinical and laboratory evaluations

One certified laboratory performed all hematology and chemistry measurements. Local laboratories could be used for repeat testing requiring for safety assessments.

Statistical analyses

Sample Size Calculations: A study with 525 patients per treatment group would have 90% power (α= 5% two-sided) to detect a difference of 10% in response to treatment.

Primary Efficacy Analysis: Treatment responses (loss of detection of HCV-RNA at 6 months after the end of treatment) would be analyzed using a logistic regression model with main effects due to treatment, genotype (type1 vs. all others), and presence of cirrhosis. Viral genotype and presence of cirrhosis were two stratification variables. A step-down procedure would be used to conserve the α at 0.05. The primary comparison would be PEG 1.5/R versus I/R using p=0.05 (two-sided) as the level of significance. If this comparison was significant, then the comparison of PEG 0.5/R versus I/R would be made. The primary analysis would be performed using data from patients randomized and receiving at least one dose of study treatment. Confirmatory analyses would be performed using data from all randomized patients.

Secondary Efficacy Analyses: Pair-wise treatment differences would be examined using logistic regression for the following endpoints listed in order of importance.

Proportion of patients with normalization of ALT at 24 weeks of follow-up.
Proportion of patients with undetectable HCV-RNA at the end of treatment.
Proportion of patients with normalization of ALT at the end of treatment.

MAJOR PROTOCOL AMENDMENTS

Change in administration of ribavirin

An amendment dated 07/13/99 imposed the requirement that ribavirin be taken with food. This was based on results of PK/PD studies that showed an increase in ribavirin absorption (AUC_{tf} and C_{max} increased by 70%) in the presence of food (a high-fat meal). Given the relationship that exists between ribavirin dose and the toxicity and perhaps activity of ribavirin, patients and physicians should be informed of the large effect of food on the absorption of ribavirin. Additional studies will be needed to confirm and characterize the effects of food on single-dose ribavirin absorption (e.g. effects of high fat vs. high non-fat caloric intake) and achievement of steady state after multiple dosing of ribavirin.

RESULTS

The study began on February 1,1999, and ended on October 6, 2000.

STUDY CENTERS

Clinical Investigators from 62 clinical centers participated in the study. The US contributed approximately half of the total study centers and approximately 2/3 of total study patients. The non-US centers were located in the following regions. Participating centers from the Americas were located in Canada (6 centers), and Argentina (2 centers). Participating centers from Europe were located in: France (8 centers), Germany (5 centers), Spain (4 centers), Sweden (2 centers), Austria (2 centers), and Greece (1 center).

PATIENT DISPOSITION

Approximately 500 patients per treatment group were randomized and received at least one dose of study treatment (see **Table 3**). Fifty patients were randomized but received no treatment; the highest number of these patients was in the interferon/ribavirin treatment arm. Approximately 20% of patients across all treatment groups did not complete the study.

Table 3. Disposition of All Randomized Subjects

Disposition	Treatment Groups			Totals
	Peg-IFN 1.5µg/kg Riba 800 mg	Peg-IFN 0.5µg/kg Riba1000/1200 mg	IFN $3x10^6$ U Riba1000/1200 mg	
Randomized	524	530	526	1580
Randomized and treated	511 (98)	514 (97)	505 (96)	1530
Randomized but not treated	13	16	21	50
Completed treatment	411 (80)	422 (82)	397 (79)	1230
Completed treatment and follow up	399 (78)	412 (80)	387 (77)	1198

Numbers in parentheses are percentages

The main reason for the non-treatment of randomized subjects was a decision of the subject not to participate in the study after the treatment allocation for this open-label study became known. The proportion of patients (20%) who did not complete the study was high but in line with other studies of interferon alpha. Most of these patients were discontinued from treatment due to adverse events (see safety data).

PATIENT DEMOGRAPHICS

Age, gender, ethnic origin, and body weight were evenly distributed across treatment groups (see **Table 4**).

Table 4. Demographics

	PEG 1.5/R	PEG 0.5/R	I/R
Age (years)			
Mean	44	44	43
Range	21-68	22-67	22-68
Gender			
Women	190 (37)	168 (33)	169 (34)
Men	321 (63)	346 (67)	336 (66)
Ethnic origin			
Caucasian	465 (91)	453 (88)	448 (89)
Black	22 (4)	28 (5)	25 (5)
Asian	5 (1)	5 (1)	8 (2)
Hispanic	12 (2)	23 (4)	13 (3)
Other	7 (1)	5 (1)	11 (2)
Body Weight (kg)			
Mean	82	83	82
Range	43-159	38-181	43-163

Numbers in parentheses are percentages

The mean age of study participants was approximately 44 years and this mean is within the age group (30-49 years of age) with the highest HCV prevalence in the US. The study protocol excluded pediatric patients. The upper age limit for the study was 70 years due to generally less favorable risk/benefit of interferon alphas in patients with advanced age. Very few elderly subjects were studied.

The mean body weight of participants was approximately 82 kg and ranged from 38 to 181 kg. The distribution towards larger body weights and the wide range in weights resulted in a wide range of exposures to ribavirin. In contrast to the weight-adjusted administration of interferon and peginterferon, ribavirin as per protocol was weight-adjusted either crudely (based on body weight above or below 75 kg) or not at all (the latter in the PEG 1.5/R group).

Approximately 2/3 of the participants were men. This gender distribution is consistent with the higher prevalence of HCV in men. Approximately 90% of participants were of Caucasian origin. Since the prevalence of HCV in the US is higher in African Americans and in Hispanics compared to Caucasians, these two ethnic minorities were under-represented in the study.

DISEASE CHARACTERISTICS AT BASELINE

Source of HCV infection

The source of HCV infection and the duration of infection were similar across treatment groups (see **Table 5**). The main source of HCV in the participants of the study was parental exposure. This is consistent with what is still the main mode of transmission of HCV, namely injection of illicit drugs. The second highest source of HCV in the participants was transfused blood products reflecting the relatively high incidence of infection before HCV screening of blood products became available. Approximately 15% of participants had other causes or non-recognized sources of infection.

Table 5. Source of HCV Infection

	PEG1.5/R	PEG 0.5/R	I/R
Transfusion products	114 (22)	105 (20)	101 (20)
Parenteral	315 (62)	337 (66)	326 (65)
Sporadic/other	82 (16)	72 (14)	78 (15)

Numbers in parentheses are percentages

Duration of HCV infection

In the participants for whom information on exposure was available, the duration of infection was estimated from the time of exposure to a source of HCV. The mean duration of infection was approximately 19 years in the three treatment groups. The duration ranged from less than 1 year to 51 years (see **Table 6**).

Table 6. Duration of Infection

	PEG1.5/R N=439	PEG 0.5/R N=449	I/R N=432
Years from exposure	20 (<1 - 51)[1]	19 (<1 - 48)	19 (<1 - 47)

[1]Means (range)

Viral genotype and viral load

Approximately two thirds of participants in the study were infected with genotype 1 and this is consistent with the incidence of this genotype in infected patients in the US. Infection with genotypes 4-6 was rare.

No relationship has been shown between rate of progression or severity of liver disease and the HCV genotype or the number of circulating HCV-RNA copies. Both viral genotype and load are known predictors of response to interferon treatment. Patients infected with viral genotype 1 and high viral load (defined as > $2X10^6$ RNA copies/ml serum) are least likely to respond to interferon treatment. The proportion of patients with these two specific prognostic viral characteristics was similar in the three treatment groups (see **Table 7**).

Table 7. Viral Genotype and Viral Load at Baseline

	PEG 1.5/R N=511	PEG 0.5/R N=514	I/R N=505
HCV genotype			
1	348 (68)	349 (68)	343 (68)
2	83 (16)	71 (14)	65 (13)
3	64 (12)	82 (16)	81 (16)
4	15 (3)	9 (2)	15 (3)
5	1 (<1)	1 (<1)	0
6	0	2 (<1)	1 (<1)
HCV RNA copies/ml			
$\leq 2 \times 10^6$	160 (31)	169 (33)	161 (32)
$>2 \times 10^6$	351 (69)	345 (67)	344 (68)

Numbers in parentheses are percentages

Severity of liver disease at baseline

Evidence of active liver disease that is progressing towards cirrhosis is generally required for interferon treatment. With rare exceptions participants at baseline had elevated levels of transaminases and evidence of liver fibrosis on liver biopsy. A baseline liver biopsy was missing in 5-8 percent of patients.

Five to seven percent of patients had compensated cirrhosis. Patients with cirrhosis are less likely to respond to interferon treatment. The presence of decompensated cirrhosis is a contraindication to interferon treatment. Around 20% of patients had evidence of bridging of portal and central veins by fibrous tracts. Thus around 25% of the participants had evidence of advanced liver disease (bridging fibrosis or cirrhosis) by liver biopsy. The biopsy also showed evidence of active inflammation and necrosis. As with other disease characteristics there was no imbalance between groups in the severity of liver disease (see **Table 8**).

Table 8. Severity of Liver Disease at Baseline

	PEG(1.5)/R N=511	PEG 0.5/R N=514	I/R N=505
ALT/ALT-ULN			
Mean	3	3	3
Range	<1-13	1- 20	1-22
Hepatic fibrosis			
None	8 (2)	0	7 (1)
Portal	325 (64)	345 (67)	329 (65)
Bridging	102 (20)	114 (22)	109 (22)
Cirrhosis	34 (7)	32 (6)	23 (5)
Missing	42 (8)	23 (5)	37 (7)

Numbers in parentheses are percentages. ULN: Upper Limit of Normal.

The sponsor determined that after taking into account protocol-required dose-modifications the compliance to study treatments was very high.

PRIMARY EFFICACY ANALYSES

The primary efficacy analysis was a logistic regression analysis with main effects due to treatment, genotype (dichotomized as genotype 1 vs. non-1), and presence of cirrhosis at baseline. The primary comparison was between the PEG 1.5/R and the I/R groups. The intent-to-treat population for the efficacy analyses was defined as randomized patients who received at least one dose of study treatment.

ITT analyses using all randomized patients gave results similar to those using the protocol-defined ITT population. The absolute difference in the proportion of responders between PEG 1.5/R and I/R was 6%. Treatment responses using both efficacy populations are shown in **Table 9.**

Table 9. Treatment Response at Week 24 Post-treatment

HCV RNA	Treatment Groups		
	Peg-IFN 1.5 Riba 800	Peg-IFN 0.5 Riba 1000/1200	IFN $3x10^6$ U Riba1000/1200
		Randomized Patients	
Negative	264 (50)	239 (45)	231 (44)
Positive	185 (35)	214 (40)	203 (39)
Missing	75 (14)	77 (15)	92 (17)
TOTAL	524	530	526
		Randomized Treated Patients	
Negative	264 (52)	239 (46)	231 (46)
Positive	185 (36)	214 (42)	203 (49)
Missing	62 (12)	61 (12)	71 (14)
TOTAL	511	514	505

Response is defined as loss of HCV RNA detection. The numbers in parentheses are percentages.

A test of non-inferiority, using confidence intervals around treatment differences adjusted for the stratification factors was performed in the pre-specified statistical analysis plan. The non-inferiority margin was pre-specified to be 10% of the response rate in the standard treatment arm (I/R). Treatment response was 45.7% in the I/R group with a 10% non-inferiority margin of -4.57%. The primary comparison, namely PEG 1.5/R vs. I/R, showed a treatment difference of 6% (C.I. 0.18%, 11.6%), thus demonstrating superiority of the experimental treatment. For the comparison of PEG 0.5/R vs. I/R, the treatment difference was 1% (C.I. – 4.7%, 6.5%). An unadjusted analysis using an overall comparison of treatment responses in the three groups showed no significance (P = 0.1), while a comparison of the PEG 1.5/R vs. the I/R group showed marginal significance (P = 0.06). Controlling for viral genotype at baseline resulted in a P value of 0.03 for the comparison between the PEG1.5/R and the I/R groups while controlling for baseline cirrhosis did not affect the P value.

SECONDARY EFFICACY ANALYSES

ALT Normalization; HCV RNA at end of treatment

The normalization of serum ALT (biochemical response) at the end of the follow up period was the principal secondary endpoint. The estimates of treatment response using ALT measurements are consistent with the results obtained using HCV RNA detection (see **Table 10**).

Table 10. Normalization of Serum ALT

	PEG (1.5)/R	PEG 0.5/R	I/R
End of Follow Up	54%[1] (274)	48% (247)	47% (236)
End of Treatment	65% (332)	63% (326)	69% (350)

[1]Proportion of patients with normalization of ALT

Virologic responses and biochemical responses at the end of treatment period were the two other pre-specified secondary outcomes. The proportion of patients with normalization of ALT at the end of the treatment period was not higher in the peginterferon-treated groups (see **Table 10**). On the other hand, the proportion of patients with undetectable

HCV RNA at the end of the treatment period was higher in the PEG1.5/R arm compared to the I/R arm (see **Table 11**). As shown in previous studies, after discontinuation of treatment a number of patients experience a relapse of the infection and HCV RNA becomes again detectable.

Table 11. Loss of Detection of HCV RNA at the End of the Treatment Period

HCV RNA Wk 48 End of treatment	PEG (1.5)/R N	PEG 0.5/R N	I/R N
Negative	333	289	271
Positive	158	202	202
Missing	33	39	53
Total	524	530	526
RESPONDERS	64%	55%	52%

The cross correlation between virologic response (loss of detection of HCV-RNA) and biochemical response (normalization of ALT levels) at the end of the follow up period was very high (not shown).

Liver histopathology

Another secondary outcome of interest was improvement in liver histopathology at 24-week post-treatment. Paired liver biopsies were obtained before and after treatment in 68% of patients. Response to treatment based on Histologic Activity Score (a measure of inflammatory changes in the liver) was defined as $\geq$2 point decrease in score from baseline. Approximately two thirds of patients in all treatment groups were observed to have a modest reduction in inflammation compared to baseline (see **Table 12**). Approximately 20% of patients had no change in inflammation score, and 10% had an increase $\geq$2 points in inflammation score. There were no differences between treatment groups.

Response to treatment based on Knodell IV score (a measure of liver fibrosis) was observed in about 20% of patients in all treatment groups. Approximately 70% of patients had no change in fibrosis score and 10% of patients had an increase in fibrosis score. There were no differences between treatment groups.

Table 12. Liver Inflammation and Fibrosis at 24 Weeks Post-Treatment

	PROPORTION OF PATIENTS WITH LOWER SCORES COMPARED TO BASELINE		
	PEG 1.5/R N= 339	PEG 0.5/R N=361	I/R N=334
Inflammation (HAI I-III score)	68%	70%	69%
Fibrosis (HAI IV)	21%	19%	20%

Health-related quality of life was assessed by a self-administered questionnaire. Scores for all groups decreased numerically during treatment and returned to baseline at the end of the post-treatment observation period. No significant differences were observed.

SUBGROUP ANALYSES

Subgroup analysis: patients who relapse in the post-treatment period

Patients with HCV-RNA undetectable at the end of treatment but detectable at 24 weeks post-treatment were considered to have relapsed. The proportion of patients who relapsed (had positive or missing HCV RNA) appeared to be numerically highest (21%) in the Peg 1.5/R group (see **Table 13**).

Table 13. Relapse in Patients with Undetectable HCV RNA at End of Treatment

HCV RNA at week 24 post-treatment	PEG 1.5/R N= 333	PEG 0.5/R N=289	I/R N=271
Positive	48	37	33
Missing	23	13	8
Negative	262	239	230
Relapsed[1]	21%	17%	15%

[1]Relapsed = Positive+ Missing/Total

Across all treatment groups, the incidence of relapse (at the end of the 24-week post-treatment period) was numerically higher (2 to 3-fold) in patients with HCV genotype 1 compared to patients with other HCV genotypes. The proportion of treatment-naïve patients who relapse after interferon monotherapy is high (around 50%). The proportion of naïve patients who relapse after interferon/ribavirin therapy is much lower and this study confirmed that observation.

Subgroup analysis: time to first loss of HCV RNA in treatment responders

The proportion of treatment responders who achieve loss of HCV RNA by week 12 of treatment is approximately 90% in the I/R group and 95% in the Peg/R groups. By week 24 nearly all treatment responders were HCV- RNA negative. The rare treatment responder who was still HCV positive by week 24 had low circulating levels of virus ($<1.5x10^6$).

Subgroup analysis: treatment response by viral genotype and load at baseline.

Patients with viral genotype 1, regardless of viral load, had a lower response rate compared to patients with other viral genotypes. Patients with high viral load ($>2x10^6$ copies of HCV RNA/ml serum) also had lower response rates compared to patients with low viral load (see **Table 14**).

Table 14. Response to Treatment by Viral Genotype and Viral Load

	PEG 1.5/R	I/R
Genotype 1	141/348 (41%)[1]	112/343 (33%)
Genotype 2-6	123/163 (75%)	119/162 (73%)
Viral load ≤ $2x10^6$/ml	121/160 (75%)	89/161 (55%)
Viral load >$2x10^6$/ml	143/351 (41%)	142/344 (41%)

[1]Proportion of responders

Patients with both genotype 1 and high viral load were least likely to respond both in the PEG 1.5/R group (30%, 78/256) and in the I/R group (29%, 71/247). Data from this study and previous studies show that patients in certain subgroups (e.g. non-genotype 1 with or without low viral titers; genotype 1 and low viral titers) have: 1) higher proportion of responders, and 2) early (≤ 3 months) and stable loss of HCV RNA in a very high proportion of treatment responders. These observations suggest that treatment duration < 12 months is likely to be efficacious and safer in these patient subgroups. A study of a shorter duration of peginterferon/ribavirin treatment in naïve patients with low viral titers at baseline, or HCV genotypes 2 and 3.

Subgroup analysis: response to treatment by presence of hepatic fibrosis

Patients with advanced hepatic fibrosis (bridging fibrosis or cirrhosis and scores of 3 or 4 respectively in Knodell's HAI IV) had numerically lower response rates compared to patients with mild or no fibrosis (scores of 0-1). The number of patients with cirrhosis (score of 4) was too low to draw conclusions on treatment responses in this subgroup; 5-8% of patients had missing biopsies at baseline.

In two of the larger subgroups, the responses to treatment across the three study arms tended to favor PEG 1.5/R (see **Table 15**).

Table 15. Response to Treatment by Presence of Advanced Hepatic Fibrosis

	Histologic Activity Index IV		
	0-1	3-4	4
PEG 1.5/R	180/333 (54)[1]	60/136 (44)	11/34 (32)
PEG 0.5/R	170/345 (49)	63/146 (43)	14/32 (44)
I/R	161/336 (48)	53/132 (40)	11/23 (46)

[1]Proportion of responders

Subgroup analysis: response to treatment by age, gender, and ethnic group

Age of Study Subjects.

In general, younger patients appeared to respond better than older patients (see **Table 16**). The study did not include sufficient numbers of subjects aged 65 and over, however, to determine whether geriatric patients respond differently than younger subjects. No pediatric subjects were studied.

Table 16. Response to Treatment by Age

	≤35[1]	35-44	45-54	55-64	≥65
PEG1.5/R	39/62 (63)	115/216 (53)	90/187 (48)	19/42 (45)	1/ 4 (25)
I/R	48/72 (67)	82/200 (41)	79/191 (41)	21/39 (54)	1/3 (33)

[1]Years of age. The numbers in parentheses are percentage of responders

Gender and Ethnic Origin.
Treatment response rates with PEG-Intron/REBETOL were 49% in men and 56% in women. Response rates were lower in African American and Hispanic patients and higher in Asians compared to Caucasians. Although African Americans had a higher proportion of poor prognostic factors compared to Caucasians the number of non-Caucasians studied (11% of the total) was insufficient to allow meaningful conclusions about differences in response rates after adjusting for prognostic factors.

Subgroup Analysis: response to treatment by geographic region
Approximately two third of study patients were enrolled in the US. The other patients were enrolled in Europe, Canada and Argentina. **Table 17** shows that overall the proportion of responders was numerically higher in patients enrolled at non-US centers compared to patients at US centers. In the I/R arm the difference in treatment response between US and non-US centers was significant. The difference was significant even after adjusting for HCV genotype and titer, liver fibrosis, and body weight. For patients enrolled in the US the proportion of responders was highest in the Peg 1.5/R arm. The odds ratio for the difference in treatment response between the I/R and Peg 1.5/R arms in the US was 0.66 (C.I. 0.49 – 0. 9) reflecting the lower likelihood of patients in the Peg 1.5 arm to remain HCV-RNA positive. In patients enrolled in non-US centers the treatment responses between study arms were not different.

Table 17. Proportion of Responders by Geographic Region

	PEG 1.5	PEG 0.5	I/R
US	169/346 (49%)	154 /343 (45%)	131/337 (39%)
Non-US	95/165 (57%)	85/171 (50%)	100/168 (59%)

Subgroup analysis: treatment response by body weight
The distribution of body weights in patients in the US was different than that of patients in other regions. The body weights in the two regions were grouped by quartiles for the analysis of response to treatment shown in the **Tables 18-19.**
Differences in response rates between treatment arms varied somewhat with body weight. Patients with lower body weight tended to have higher response rates than patients with higher body weights.

Table 18. Treatment Response by Baseline Weight in Patients in US Centers

Body weight quartiles (kg)	PEG 1.5/R	PEG 0.5/R	I/R	Total[1]
≤ 74	51/93 (55)	41/89 (46)	28/75 (37)	257
>74 ≤85	45/86 (52)	34/79 (43)	40/92 (43)	260
>85 ≤98	37/86 (43)	38/78 (49)	46/97 (47)	261
> 98	36/81 (44)	42/94 (45)	17/74 (23)	249

[1]Number of patients in each weight group. Numbers in parentheses are percentage of responders

Table 19. Treatment Response by Baseline Weight in Patients in non-US Centers

Body weight quartiles (kg)	PEG 1.5/R	PEG 0.5/R	I/R	Total[1]
≤ 64	25/36 (69)	23/45 (51)	32/61 (52)	132
>64 ≤74	23/42 (55)	25/43 (58)	29/40 (72)	125
>74 ≤84	21/40 (52)	18/38 (47)	22/44 (50)	122
> 84	26/47 (55)	19/45 (42)	17/33 (52)	125

[1]Number of patients in each weight group. Numbers in parentheses are percentage of responders

A number of factors could account for this apparent interaction between body weight and treatment response. The different response rates may, for example, be due to differences in exposure to study drugs due to insufficient or no adjustment of dose for body weight. In the PEG1.5 group patients received a fixed dose (800 mg) of ribavirin, in the IFN/R group patients received a fixed dose of interferon.

To explore this issue further the sponsor analyzed treatment response by daily dose of ribavirin normalized by body weight (mg/kg). Logistic regression analyses showed that the probability of response was a function of ribavirin daily dose per body weight. From these analyses the sponsor concluded that 13± 2 mg/kg is the optimal dose of ribavirin to administer with peginterferon 1.5 μg/kg. The sponsor analyzed the response rate in the PEG1.5/R group using as a cutoff a daily dose of ribavirin of 10.6 mg/kg. The selection was arbitrarily based on the dose a patient with "average" body weight (75 kg) would receive. These analyses showed that treatment responses were numerically higher in patients who received more than 10.6 mg/kg/day of ribavirin.

In the ——— study, interferon-naïve subjects were treated for 6 months with either 800 or 1000/1200 mg/day of ribavirin in combination with INTRON A. The sustained response rate was numerically higher in the INTRON A + ribavirin 1000/1200 mg/day group compared to the INTRON A + ribavirin 800 mg/day group (27% vs. 23%). An analysis was done with subjects categorized as being on 'high' or 'low' ribavirin regimens depending on whether they received more or less than 11 mg/kg/day of ribavirin. The 11mg/kg break point was selected as it represents a dose of approximately 800 mg for an "average weight" (75 kg) subject. Using this categorization, the sustained response rates were 31% and 22% for 'high' and 'low' ribavirin regimens.

Based on these exploratory analyses of the present efficacy trial and other trials, the sponsor proposed that ribavirin be administered on a weight-adjusted basis to patients with chronic hepatitis C (see **Table 20**).

Table 20. Sponsor's Proposal for REBETOL Dosing

Body weight kg (lbs)	REBETOL mg/day	REBETOL Number of Capsules
<40 (<88)	800	2 x 200 mg capsules AM, 2 x 200 mg capsules PM
40-64 (88-142)	800	2 x 200 mg capsules AM, 2 x 200 mg capsules PM
65-85 (143-188)	1,000	2 x 200 mg capsules AM, 3 x 200 mg capsules PM
86-105 (189-231)	1,200	3 x 200 mg capsules AM, 3 x 200 mg capsules PM
>105 (>231)	1,400	3 x 200 mg capsules AM, 4 x 200 mg capsules PM

The sponsor analyzed safety data based on a dichotomized ribavirin dose ($\leq$ 10.6 or > 10.6 mg/kg). These analyses showed that the incidence of adverse events known to be induced by ribavirin (e.g. anemia) was numerically higher in the > 10.6 mg/kg group. The incidence of adverse events not attributable to ribavirin (e.g. neutropenia) was also numerically higher in the >10.6 mg/kg subgroup group. Moreover, the incidence of dose modifications for adverse events was also higher in this subgroup.

The sponsor provided a rationale for weight-based ribavirin dosing based on post-hoc analyses of the efficacy data. It could not be determined from a review of the sponsor's analyses why a 13$\pm$2 mg/kg ribavirin dosage was judged to be optimal. It was also unclear why the sponsor had proposed doses $\geq$16 mg/kg in patients weighing $\leq$50 kg. The agency determined that the sponsor did not provide an adequate pharmacokinetic and risk/benefit justification for the doses of ribavirin he proposed.

Exploratory analysis: treatment response by ribavirin dosage (mg/kg) For these exploratory analyses the patients in the study were categorized arbitrarily by dividing the distribution of ribavirin dosages into quartiles. Caution is needed in interpreting the results of these analyses because of small patient numbers and imbalance in the patient numbers between quartiles and across study arms within the same quartile. More importantly, the comparison of the outcome data by ribavirin dosage may be confounded by differences known (e.g. body weight) or unknown between these non-randomized groups.

Treatment responses by ribavirin dose administered/ body weight /day were examined in the patient subgroups shown in **Table 21.** All treated patients were included in the analyses. The proportion of responders was higher in subgroups with higher ribavirin dose/weight ratios.

Table 21. Treatment Response by Ribavirin Dosage

Ribavirin dosage quartiles	PEG 1.5/R	PEG 0.5/R	I/R
> 14.7[1]	13/21 (62)[2]	76/171 (44)	99/184 (54)
>13.3 - ≤ 14.7	25/38 (67)	91/174 (52)	75/170 (44)
≥10.7 - ≤ 13.3	70/126 (56)	58/134 (43)	50/126 (40)
<10.7	156/326 (48)	14/35 (40)	7/25 (28)
Ribavirin dosage median (range)	9.8 (5-19)[3]	13.9 (7-26)	14.2 (7-23)

[1] mg/kg (daily ribavirin dose/body weight at baseline). [2] Percentage of responders.
[3] Numbers are medians, minimum and maximum values in mg/kg

The proportion of responders was higher in the higher ribavirin dose groups even after controlling for HCV genotype, high or low HCV RNA, and gender in the analyses (not shown).

Exploratory analysis: safety outcomes by ribavirin dosage (mg/kg)
The potential for higher numbers of treatment responders with higher ribavirin doses must be considered together with the potential for higher ribavirin toxicity.

Dose Modification or Discontinuation of Study Treatment
The incidence of dose modification due to adverse events was numerically higher in patients in the PEG1.5/R and the I/R arms who had higher daily ribavirin dose/body weight ratios (see **Table 22**). Patients who discontinued treatment due to adverse events were not included in this analysis.

Table 22. Modification of Dose of Study Treatment by Ribavirin Dosage and Treatment Group

Ribavirin dosage mg/kg/day	PEG 1.5/R	PEG 0.5/R	I/R
> 14.7	8 (47)[1]	57 (40)	65 (41)
>13.3 - ≤ 14.7	31 (61)	70 (32)	68 (31)
≥10.7 - ≤ 13.3	54 (45)	44 (36)	33 (31)
<10.7	124 (38)	14 (44)	4 (18)

[1] Number (percentage) of patients with reduction of interferon or ribavirin dose

Table 23 shows that the in the PEG 1.5/R arm, the incidence of dose modification appeared to be numerically higher in the higher ribavirin dosage subgroups in the following body systems: CNS/PNS, endocrine, blood clotting, RBC, WBC and skin. The number of events is small and interpretation must be cautious.

Table 23. Modification of Dose of Study Treatment by Ribavirin Dosage and Body System in the PEG 1.5/R Arm.

Body system	Ribavirin Dosage mg/kg/day			
	<10.7	≥10.7 ≤ 13.3	>13.3 ≤ 14.7	> 14.7
Application Site	0	0	1 (2)	0
Body as a Whole	29 (9)[1]	15 (13)	3 (6)	1 (6)
CNS/PNS	8 (2)	4 (1)	1 (1)	3 (6)
Endocrine	1 (0.3)	1 (1)	1 (2)	0
Heart Rate/ Rhythm	1 (0.3)	0	1(2)	0
Musculoskeletal	7 (2)	3 (3)	0	0
Platelet Bleeding/Clotting	12 (4)	7 (6)	4 (8)	1 (6)
Psychiatric	12 (4)	7 (6)	4 (8)	1 (6)
Red Blood Cell	22 (7)	12 (10)	8 (16)	2 (12)
Resistance Mechanism	2 (0.6)	4 (3)	0	0
Respiratory	5 (2)	1 (1)	1 (2)	0
Skin/Appendage	7 (2)	2 (2)	2 (4)	1 (6)
Vision	2 (0.6)	1 (1)	0	0
White Cell/RES	51 (16)	26 (22)	11 (22)	4 (24)

[1] Number (percentage) of patients

Table 24 shows numerically higher incidence of dose modifications across all three study arms in the higher ribavirin dosage groups (mg/kg/day) for anemia and neutropenia.

Table 24. Modification of Dose of Study Treatment for Hematologic Toxicity by Ribavirin Dose and Study Arm

Ribavirin dose (mg/kg/day)	PEG 1.5/R	PEG 0.5/R	I/R
Anemia			
> 14.7	2 (12)[1]	29 (40)	31(20)
>13.3 - ≤ 14.7	8 (16)	24(11)	28(13)
≥10.7 - ≤ 13.3	12 (10)	9 (7)	7 (7)
<10.7	22 (7)	2 (6)	1 (5)
Neutropenia			
> 14.7	4 (24)	14 (10)	17 (11)
>13.3 - ≤ 14.7	10 (20)	21 (10)	15 (7)
≥10.7 - ≤ 13.3	26 (22)	12 (10)	6 (6)
<10.7	51 (16)	2 (6)	0

Numbers in parentheses are percentages

The overall incidence of dose discontinuation was numerically similar across ribavirin dose groups and study arms. Discontinuations for anemia and neutropenia were numerically higher in the higher ribavirin doses in the three study arms (not shown).

Adverse Events by Ribavirin Dosage
The incidence of anemia and neutropenia was numerically higher in the higher ribavirin dose subgroups (mg/kg/day) across the three study arms. The incidence of thrombocytopenia appeared to also follow the same upward trend with higher ribavirin dose in the PEG1.5/R and the I/R arms of the study (see **Table 25**).

Table 25. Incidence of Hematologic Adverse Events by Ribavirin Dosage and Study Arms

Ribavirin dosage mg/kg/day	PEG 1.5/R		PEG 0.5/R		I/R	
	All grades	Severe/ LT[1]	All grades	Severe/ LT	All grades	Severe/ LT
	anemia					
> 14.7	3 (18)	0	40 (28)	2 (1)	41 (26)	3 (2)
>13.3 - ≤ 14.7	16 (31)	1 (2)	32 (15)	1 (0.5)	35 (16)	0
≥10.7 - ≤ 13.3	15 (13)	0	14 (12)	0	8 (8)	0
<10.7	27 (8)	0	3 (9)	1 (3)	2 (9)	0
	neutropenia					
> 14.7	8 (47)	4 (24)	29 (20)	9 (6)	30 (19)	9 (6)
>13.3 - ≤ 14.7	15 (29)	6 (12)	27 (12)	12 (5)	28 (13)	10 (5)
≥10.7 - ≤ 13.3	37 (31)	14 (12)	20 (17)	9 (7)	10 (9)	4 (4)
<10.7	74 (23)	28 (9)	2 (6)	2 (6)	1 (5)	0
	thrombocytopenia					
> 14.7	1 (6)	0	2 (1)	0	6 (4)	0
>13.3 - ≤ 14.7	4 (8)	0	2 (1)	0	3 (1)	0
≥10.7 - ≤ 13.3	3 (3)	0	4 (3)	1 (1)	1 (1)	0
<10.7	20 (6)	0	3 (9)	0	0	0

[1] Life-threatening. Numbers in parentheses are percentages

The safety data suggest that with increasing ribavirin dosage higher proportions of patients experience adverse events. There may be a breakpoint in the increase in toxicity at ribavirin dosages >13 mg/kg/day. At these dose levels for example the majority of patients (around 60%) required dose modification for adverse events. The rise in incidence of hematologic toxicities (anemia, neutropenia, and thrombocytopenia) seems also steeper at >13 mg/kg/day of ribavirin dosage.

The schedule of clinical and laboratory assessment of patients during the trial was optimal and the protocol contained conservative rules for dose modification for a number of well known potentially serious and life-threatening adverse events induced by interferon and ribavirin (e.g. neutropenia and anemia). As is true for other clinical conditions, therapy of patients with chronic hepatitis C is likely to be less rigidly controlled and more uneven outside of clinical trials. For these reasons the incidence of toxicities in the post-marketing phase may be higher than that observed in the clinical trial phase because of lower incidence and/or less timely dose-modifications for adverse events. The weight-based ribavirin dosing proposed by the sponsor may reasonably be expected to further increase the incidence of adverse events.

In view of the dose-dependent toxicities of ribavirin more studies are needed to optimize the ribavirin dose. Patients with lower than average body weight should be followed carefully for interferon and ribavirin-induced toxicities.

SAFETY ANALYSES

Discontinuation of study treatment

Adverse events were the main reason for discontinuation of study treatment. The incidence of all-cause discontinuation was numerically lower in the second half of the treatment period (see **Table 26**).

Table 26. Reasons for Treatment Discontinuation Before and After Six Months of Treatment

	Treatment Groups		
Disposition	**PEG 1.5/R** N=511	**PEG 0.5/R** N=514	**I/R** N=505
Discontinued by six months	**69 (14)**	**56 (11)**	**66 (13)**
Death	0	1 (<1)	1 (<1)
Other adverse event	51 (10)	43 (8)	36 (7)
Loss to follow-up	6 (1)	3 (<1)	7 (1)
Subject's choice	9 (2)	4 (<1)	15 (3)
Non-compliance	3 (<1)	4 (<1)	6 (1)
Non-eligibility	0	0	1 (<1)
Administrative	0	1 (<1)	0
Discontinued after six months	**31 (6)**	**36 (7)**	**42 (8)**
Adverse event	23 (5)	25 (5)	29 (6)
Loss to follow-up	2 (<1)	3 (<1)	6 (1)
Subject's choice	3 (<1)	6 (1)	4 (<1)
Non-compliance	3 (<1)	2 (<1)	3 (<1)

Overall 13-14% of patients discontinued therapy. The most common reasons for discontinuation of therapy were because of psychiatric, constitutional (fatigue, headache), or gastrointestinal adverse events.

Dose reduction of interferon alfa-2b was related to dose (PEG-Intron 1.5 μg/kg > PEG-Intron 0.5 μg/kg or INTRON A), 40%, 27%, 28%, respectively. Dose reduction for ribavirin was similar across all three groups, 33-35%. The most common reasons for dose

modifications were neutropenia (8-18%), and anemia (9-13%). Other reasons included depression (2-3%), fatigue (2-4%), nausea (2-4%), and thrombocytopenia (1-3%). See also analyses of ribavirin dose subgroups on **pages 34-38**.In many but not all cases, adverse events resolved after dose reduction or discontinuation of therapy. Some patients experienced ongoing or new serious adverse events during the 6-month follow-up period; 13 patients experienced life-threatening psychiatric events (suicidal ideation or attempt) and one patient accomplished suicide.

Serious adverse events

There were two deaths: one suicide in a patient receiving peginterferon/ribavirin and one death in the Interferon/ribavirin group (motor vehicle accident). The incidence of serious adverse events was 17% in the PEG-Intron/REBETOL groups and 14% in the INTRON A/REBETOL group. Three-hundred and twenty-two SAEs were reported in 172 subjects and 241 of these were reported during treatment. The most frequently reported SAEs for all groups were listed in the following body systems (see **Table 27**).

Table 27. Selected Serious Adverse Events by Body System

	Body as a Whole	Psych-iatric	G I	Resist. Mech.	Vision	Respir.	Musculo -skeletal	Endo-crine
PEG 1.5	18 (4)	12 (2)	17 (3)	11 (2)	5 (1)	4 (0.8)	6 (1)	3 (0.5)
PEG 0.5	14 (3)	24 (5)	6 (1)	3 (0.6)	7 (1.4)	6 (1)	3 (0.6)	2 (0.4)
I/R	16 (3)	14 (3)	16 (3)	1 (0.2)	2 (0.4)	3 (0.6)	1 (0.2)	0

Serious Infections:

Nine subjects reported fifteen serious infections that were classified as resistance mechanism disorders. In the PEG 1.5/R group six subjects reported eleven infectious events. In the PEG 0.5/R group two subjects reported three infectious events. Some of the serious infections were associated with neutropenia. Other serious adverse events with presumed infectious etiology (in whole or in part) are listed under Other Body Systems in **Table 28**. The overall number of serious infections appears to be related to interferon exposure (PEG1.5 > PEG 0.5 > INF).

Table 28. Serious Infectious Adverse Events

	PEG 1.5/R	PEG 0.5/R	I/R
Resistance Mechanism			
Abscess	3	1	0
Cellulitis	5	1	1
Infection(bacterial, viral, or NOS).	3	0	0
Sepsis	0	1	0
Other Body Systems			
Appendicitis	4	1	0
Bronchitis	0	1	0
Pneumonia	1	1	1
Prostatitis	1	0	0
UTI	0	1	1
Total	**17**	**7**	**3**

Pregnancies:
Three study subjects became pregnant after the end of the treatment period; one of these subjects had a miscarriage and two had elective abortions. Eight partners of study subjects became pregnant during the treatment period; three of these pregnancies resulted in healthy newborns, three were terminated electively; the outcome of the other two pregnancies is unknown. Two partners of study subjects became pregnant in the post-treatment follow-up period; both pregnancies were terminated electively.

Listing of Serious Adverse Events:
Individual serious adverse events occurred at a frequency ≤1%. The events included suicide attempt, suicidal ideation, severe depression; psychosis, agitation, aggressive reaction, relapse of drug addiction/overdose; nerve palsy (facial, oculomotor); cardiomyopathy, myocardial infarction, angina, pericardial effusion, retinal ischemia, retinal artery or vein thrombosis, blindness, decreased visual acuity, optic neuritis, transient ischemic attack, supraventricular arrhythmias, loss of consciousness; neutropenia, infection (sepsis, pneumonia, abscess, cellulitis); emphysema, bronchiolitis obliterans. pleural effusion, gastroenteritis, pancreatitis, gout, weight decrease, fatigue, fever, diabetes mellitus, hyperthyroidism and hypothyroidism, autoimmune thrombocytopenia with or without purpura, rheumatoid arthritis, interstitial nephritis, lupus-like syndrome, sarcoidosis, aggravated psoriasis; urticaria, injection-site necrosis, vasculitis, phototoxicity. See Clinical Narrative Section for summaries of selected serious adverse events.

Eighty-one serious adverse events were reported during the six-month follow up period. The incidence was around 5% across treatment groups.

Life-threatening and severe adverse events
The incidence of life-threatening adverse events was ≤ 1% across all groups. The incidence of severe adverse events was 31-34% in the PEG-Intron/REBETOL groups and 23% in the INTRON A/REBETOL group.

Most common adverse events
Nearly all study patients experienced one or more adverse events. The most common adverse events were psychiatric and occurred among 77% of patients. The most common individual psychiatric events were depression, irritability, and insomnia, each reported by approximately 30-40% of subjects in all treatment groups. Suicidal behavior (ideation, attempts, and suicides) occurred in 2% of all patients during treatment or during follow-up after treatment cessation (see **Table 29**).

PEG-Intron induced fatigue or headache in approximately two-thirds of patients, and induced fever or rigors in approximately half of the patients. The severity of some of these systemic symptoms (e.g. fever and headache) tended to decrease as treatment continued. The incidence tended to be higher with PEG-Intron than with Intron A therapy alone or in combination with REBETOL.

Application site inflammation and reaction (e.g. bruise, itchiness, irritation) occurred at approximately twice the incidence with PEG-Intron therapies (in up to 75% of patients) compared with INTRON A. However injection site pain was infrequent (2-3%) in all groups. Other common adverse events in the PEG-Intron/REBETOL group included myalgia (56%), arthralgia (34%) nausea (43%), anorexia (32%), weight loss (29%), alopecia (36%), and pruritus (29%).

Table 29. Adverse Events Occurring in > 5% of Patients

Adverse Events	PEG 1.5/R	I/R
Application Site		
Injection Site Inflammation/Reaction	75	49
Autonomic Nervous System		
Mouth Dry	12	8
Sweating Increased	11	7
Flushing	4	3
Body as a Whole		
Fatigue/Asthenia	66	63
Headache	62	58
Rigors	48	41
Fever	46	33
Weight Decrease	29	20
RUQ Pain	12	6
Chest Pain	8	7
Malaise	4	6
Central/Peripheral Nervous System		
Dizziness	21	17
Endocrine		
Hypothyroidism	5	4
Gastrointestinal		
Nausea	43	33
Anorexia	32	27
Diarrhea	22	17
Vomiting	14	12
Abdominal Pain	13	13
Dyspepsia	9	8
Constipation	5	5
Hematologic Disorders		
Neutropenia	26	14
Anemia	12	17
Leukopenia	6	5
Thrombocytopenia	5	2
Liver and Biliary System		
Hepatomegaly	4	4
Musculoskeletal		
Myalgia	56	50
Arthralgia	34	28
Musculoskeletal Pain	21	19
Psychiatric		
Insomnia	40	41
Depression	31	34
Anxiety/Emotional Lability/Irritability	47	47
Concentration Impaired	17	21
Agitation	8	5

Adverse Events	PEG 1.5/R	I/R
Nervousness	6	6
Reproductive, Female		
Menstrual Disorder	7	6
Resistance Mechanism		
Infection Viral	12	12
Infection Fungal	6	1
Respiratory System		
Dyspnea	26	24
Coughing	23	16
Pharyngitis	12	13
Rhinitis	8	6
Sinusitis	6	5
Skin and Appendages		
Alopecia	36	32
Pruritus	29	28
Rash	24	23
Skin Dry	24	23
Special Senses Other,		
Taste Perversion	9	4
Vision Disorders		
Vision blurred	5	6
Conjunctivitis	4	5

*Patients reporting one or more adverse events. A patient may have reported more than one adverse event within a body system/organ class category.

Laboratory Values

Hemoglobin

REBETOL induced a decrease in hemoglobin levels in approximately two thirds of patients. Hemoglobin levels decreased to <11g/dl in about 30% of patients. Severe anemia (<8 g/dl) occurred in < 1% of patients. Dose modification was required in 9 and 13% of patients in the PEG-Intron/REBETOL and INTRON A /REBETOL groups. Hemoglobin levels become stable by treatment week 4-6 on average. Hemoglobin levels return to baseline between 4 and 12 weeks post- treatment.

Neutrophils

Decreases in neutrophil counts were observed in a majority of patients treated with PEG-Intron alone (70%) or as combination therapy with REBETOL (85%) and INTRON A/REBETOL (60%). Severe potentially life-threatening neutropenia ($<0.5 \times 10^9$/L) occurred in 1% of patients treated with PEG-Intron monotherapy, 2% of patients treated with INTRON A/REBETOL and in 4% of patients treated with PEG-Intron/REBETOL. Two percent of patients receiving PEG-Intron monotherapy and 18% of patients receiving PEG-Intron /REBETOL required modification of interferon dosage. Few patients ($\leq$ 1%) required permanent discontinuation of treatment. Neutrophil counts generally return to pre-treatment levels within 4 weeks of cessation of therapy.

Platelets

Platelet counts decrease in approximately 20% of patients treated with PEG-Intron alone or with REBETOL and in 6% of patients treated with INTRON A/REBETOL. Severe

decreases in platelet counts (<50,000/mm^3) occur in <1% of patients. One to three percent of patients required dose modification of INTRON A or PEG-Intron respectively. Platelet counts generally returned to pretreatment levels within 4 weeks of the cessation of therapy.

Thyroid Function

Development of TSH abnormalities, with and without clinical manifestations, is associated with interferon therapies. Clinically apparent thyroid disorders occur among patients treated with either Intron A or PEG-Intron (with or without REBETOL) at a similar incidence (5% for hypothyroidism and 3% for hyperthyroidism). Subjects developed new onset TSH abnormalities while on treatment and during the follow-up period. At the end of the follow-up period 7% of subjects still had abnormal TSH values.

Bilirubin and Uric acid

In the present study 10-14 % of patients developed hyperbilirubinemia and 33-38% developed hyperuricemia in association with hemolysis. Six patients developed mild to moderate gout.

OTHER SAFETY DATA

Immunogenicity

Approximately 2% of patients receiving PEG-Intron (32/1759) or INTRON A (11/728) with or without REBETOL developed low-titer (≤160) neutralizing antibodies to PEG-Intron or INTRON A. No apparent correlation of antibody development to clinical response or adverse events was observed. The incidence of post-treatment binding antibody ranged from 8 to 15 percent.

Overdosage

A few patients accidentally received a dose greater than that prescribed. There were no instances in which a patient received more than 10.5 times the intended dose of PEG-Intron. The maximum dose received by any patient was 3.45 μg/kg weekly over a period of approximately 12 weeks. There were no significant ribavirin overdosages in this study; the maximum known overdosage of ribavirin was an intentional ingestion of 10 g (fifty 200 mg capsules). There were no serious reactions attributed to these overdosages.

Concomitant medications

There was a major increase in the use of psychotherapeutics, analgesic and anti-inflammatory during the course of the treatment period consistent with the incidence of psychiatric, systemic and musculoskeletal adverse events. Use of antimicrobials, antihistaminics and dermatologic drugs also increased. There was no difference between study arms in concomitant medication usage

Adverse event reporting by geographic region

The table below shows a selected list of adverse events by geographic region in patients treated with PEG 1.5/R and I/R. Study centers in the US reported a higher number of adverse events compared to study centers from other countries.

Table 30. Selected Adverse Event Reports from US and Non-US Study Centers

Adverse event	PEG 1.5/R		I/R	
	US	Non-US	US	Non-US
Myalgia	241 (70)[1]	67 (40)	197 (58)	64 (38)
Injection site reaction	208 (61)	91 (54)	116 (34)	68 (40)
Headache	237 (70)	90 (54)	216 (63)	94 (56)
Rigors	195 (57)	52 (31)	159 (47)	49 (29)
Nausea	181 (53)	44 (26)	142 (42)	40 (24)
Fever	175 (51)	67 (40)	107 (31)	61 (36)
Insomnia	168 (49)	51 (30)	171 (50)	56 (33)
Arthralgia	155 (45)	54 (32)	138 (40)	40 (24)
Depression	131 (38)	53 (32)	135 (40)	48 (29)
Irritability	140 (41)	41 (24)	134 (39)	40 (24)
Alopecia	134 (39)	54 (32)	111 (33)	51 (30)
Anorexia	127 (37)	42 (25)	101 (30)	38 (23)
Weight decrease	92 (27)	61 (36)	64 (19)	46 (27)
Neutropenia	100 (29)	34 (20)	49 (14)	20 (12)
Anemia	46 (13)	16 (10)	58 (17)	26 (15)

[1] Numbers in parentheses are percentages

Weight decrease and asthenia were the only two adverse events with higher reporting rates by non-US centers. Regional differences in the rate of reports were observed for both symptomatic (e.g. myalgia, anorexia) and quantifiable (e. g. neutropenia, alopecia) events. The cause of these differences was not further assessed. Non-drug related causes (e.g. differences in ascertainment procedures by investigators or in spontaneous reporting by patients) may account partly or fully for the difference between regions in the number of all adverse events. The numbers of serious adverse events were too few for the purpose of this subgroups analysis; no consistent numerical differences between regions were observed.

SUMMARY AND DISCUSSION

EFFICACY OF PEGINTERFERON ALFA-2B AND RIBAVIRIN

Primary efficacy outcome: Loss of detection of HCV RNA in serum at end of follow up period.

The response to treatment with 1.5 μg/kg peginterferon-alfa 2b and 800 mg ribavirin (52%) is superior to the response to treatment with $3x10^6$ Units interferon alfa-2b and 1000 –1200 mg ribavirin (46%). The treatment difference is t 6%, (C.I. 0.18%, 11.6%).

The response to treatment with peginterferon alfa-2b (1.5μg/kg for 4 weeks then 0.5 μg/kg for 44 weeks) plus ribavirin 1000-1200 mg is not superior to the response to treatment with interferon plus ribavirin.

In the peginterferon monotherapy study the 1.5 μg/kg dose was not superior in efficacy to the 1.0 μg/kg dose and had higher toxicity. Given these observations,

the safety and efficacy of combination treatment with peginterferon 1.5 μg/kg plus ribavirin should be compared to that of peginterferon 1.0 μg/kg plus ribavirin.

The proportion of patients who relapse after the end of the treatment was highest in the PEG 1.5/R group. It is not known if the lower dose of Ribavirin (800 mg/d) was a factor.

The proportion of treatment responders who achieve loss of HCV RNA is around 90-95% by treatment week 12 and 99% by week 24. Treatment with peginterferon and ribavirin should be discontinued in patients with persistent high viral titers at 6 months of treatment.

HCV genotype 1, high levels of circulating HCV RNA ($>2x10^6$copies/ml serum), and presence of advanced liver fibrosis are associated with less favorable response to treatment.

Treatment responses are higher in patients with genotypes 2 and 3 and time to first response is shorter ($\leq$3 months) in these patients. Treatment responses are also higher in patients with low viral load ($< 2x10^6$/ml plasma). Treatment regimens of shorter duration (e.g. six months) should be evaluated in these patients.

In general, younger patients appeared to have higher response rates than older patients. No pediatric studies of peginterferon and ribavirin have been performed. Treatment responses appeared to be higher in women.

Response rates were lower in African American and Hispanic patients and higher in Asians compared to Caucasians. Although African Americans had a higher proportion of poor prognostic factors compared to Caucasians the number of non-Caucasians studied was insufficient to allow meaningful conclusions about differences in response rates. The prevalence of HCV in the US is higher in African Americans and in Hispanics compared to Caucasians, and these two ethnic minorities were under-represented in the study. Treatment responses should be studied further in these minorities.

Differences in response rates between treatment arms varied somewhat with body weight. Patients with lower body weight tended to have higher response rates than patients with higher body weights. A number of factors could account for this apparent interaction between body weight and treatment response. From the data and the analyses performed by the sponsor it could not be determined if patients with lower body weight had higher response rates because of higher exposures to ribavirin.

There is no information on treatment response in patients who have failed previous interferon alfa-2b treatment.

Secondary efficacy outcomes

Biochemical Response at End of Follow up Period.

The estimate of treatment response using normalization of serum ALT was generally consistent with the estimate using loss of detection of HCV RNA in serum.

Biochemical Response at End of Treatment Period.

The proportion of patients with normalization of serum ALT at the end of the treatment period was not higher in the peginterferon-treated groups.

Virologic Response at End of Treatment Period.

The proportion of patients with loss of detection of HCV RNA at the end of the treatment period was higher in the PEG1.5/R arm compared to the I/R arm.

Scores for Liver Inflammation and Fibrosis.

Scores for hepatic inflammation and fibrosis were not superior with peginterferon and ribavirin treatment compared to interferon and ribavirin.

Health-Related Quality of Life Scores.

The QOL scores were not improved in any of the treatment groups either during or after treatment.

Effect of food on ribavirin absorption

Ribavirin should be taken with food. Additional studies to better characterize the food effects should be performed

SAFETY OF PEGINTERFERON ALFA-2B AND RIBAVIRIN

Patients receiving PEG-Intron 1.5 μg/kg and ribavirin required dose modification more frequently compared to patients receiving interferon and ribavirin. In many but not all cases, adverse events resolved after dose reduction or discontinuation of therapy.

The incidence of serious adverse events and of severe adverse events was numerically somewhat higher in the PEG 1.5/R arm compared to I/R.

The overall number of serious infections appears to be related to interferon exposure (PEG 1.5 > PEG 0.5 > INF). In some patients serious infections were associated with neutropenia. The incidence of severe neutropenia (4% vs. 2%), and dose reduction (18% vs. 8%) and discontinuations (1% vs. 0.2%) for neutropenia were higher in the PEG 1.5/R group compared to the I/R group.

Some patients experienced ongoing or new serious adverse events during the 6-month follow-up period; 13 patients experienced life-threatening psychiatric events (suicidal ideation or attempt) and one patient accomplished suicide.

The most common adverse events were psychiatric and occurred among 77% of patients. The most common individual psychiatric events were depression, irritability, and insomnia, each reported by approximately 30-40% of subjects in all treatment groups. Suicidal behavior (ideation, attempts, and suicides) occurred in 2% of all patients during treatment or during follow-up.

PEG-Intron induced fatigue or headache in approximately two-thirds of patients, and induced fever or rigors in approximately half of the patients. The severity of some of these systemic symptoms (e.g. fever and headache) tended to decrease as treatment continued. The incidence tended to be higher with PEG-Intron than with Intron A therapy alone or in combination with REBETOL.

Application site inflammation and reaction (e.g. bruise, itchiness, irritation) occurred at approximately twice the incidence with PEG-Intron therapies (in up to 75% of patients) compared with INTRON A. However injection site pain was infrequent (2-3%) in all groups. Other common adverse events in the PEG-Intron/REBETOL group included myalgia (56%), arthralgia (34%) nausea (43%), anorexia (32%), weight loss (29%), alopecia (36%), and pruritus (29%).

Hemoglobin levels decreased to <11g/dl in about 30% of patients. Severe anemia (<8 g/dl) occurred in < 1% of patients. Hemoglobin levels become stable by treatment week 4-6 on average. Hemoglobin levels return to baseline between 4 and 12 weeks post- treatment.

Decreases in neutrophil counts were observed in a majority of patients treated with PEG-Intron with REBETOL (85%) and INTRON A/REBETOL (60%). Neutrophil counts generally return to pre-treatment levels within 4 weeks of cessation of therapy.

Platelet counts decrease in approximately 20% of patients treated with PEG-Intron with REBETOL and in 6% of patients treated with INTRON A/REBETOL. Severe decreases in platelet counts (<50,000/mm^3) occur in <1% of patients. One to three percent of patients required dose modification of INTRON A or PEG-Intron respectively. Platelet counts generally returned to pretreatment levels within 4 weeks of the cessation of therapy.

Development of TSH abnormalities, with and without clinical manifestations, is associated with interferon therapies. Clinically apparent thyroid disorders occur among patients treated with either Intron A or PEG-Intron (with or without REBETOL) at a similar incidence (5% for hypothyroidism and 3% for hyperthyroidism). Subjects developed new onset TSH abnormalities while on treatment and during the follow-up period. At the end of the follow-up period 7% of subjects still had abnormal TSH values.

Ribavirin is known to have mutagenic, genotoxic, embryocidal, and teratogenic effects. Warnings about potential carcinogenicity, and about risks of birth defects or death of the fetus should be mentioned in the package insert.

In view of the dose-dependent toxicities of ribavirin more studies are needed to optimize the ribavirin dose. Patients with lower than average body weight should be followed carefully for interferon and ribavirin-induced toxicities.

COMPARISON OF ACTIVITY AND SAFETY OF WEIGHT-BASED RIBAVIRIN ACROSS STUDY ARMS

The comparison of treatment response based on ribavirin weight-adjusted dose is a post-hoc analysis.

Due to differences in dosing regimens (see below), sorting data by ribavirin dose (mg/kg) results in subgroups that are different in numbers, body weights, and may differ in other unknown factors.

	PEG 1.5 μg/kg/wk R 800 mg/qd	PEG 0.5 μg/kg/wk R 1000-1200mg/qd	IFN 9x10^6 U/wk R 1000-1200 mg/qd
Interferon	Weight adjusted	Weight adjusted	No weight adjustment
Ribavirin	"Lower" dose. No weight adjustment	"Higher" dose. Crude weight adjustment	"Higher" dose. Crude weight adjustment

There is a modest effect of body weight on treatment response that is not consistent across study arms and subgroups.

There is an effect of body weight on adverse events (both ribavirin- and interferon-associated and on the incidence of dose-reduction due to adverse events. There is a suggestion of threshold where steeper increase in ribavirin toxicity may be seen.

Multiple other factors affect response to treatment. In multivariate regression analyses weight makes a small contribution to the model.

There are insufficient US data on safety/activity of higher exposure to ribavirin in the PEG1.5 group and also in other dose groups due to study design and to higher than expected body weights of study subjects (US mean 85 kg; ribavirin dose adjustment 1000 vs. 1200mg based on 75kg).

The sponsor's proposed weight-based scheme raised safety concerns due to high exposure of patients in certain weight subgroups.

Studies are ongoing to compare safety and efficacy of weight-based and fixed-weight ribavirin.

CONCLUSIONS

The response to treatment with 1.5 μg/kg peginteferon-alfa 2b and 800 mg ribavirin is superior to the response to treatment with 3x10^6 Units interferon alfa-2b and 1000 –1200 mg ribavirin. The treatment difference is modest.

A number of serious toxicities are associated with interferon and ribavirin treatment. There is no definitive evidence that interferon treatment of chronic hepatitis C decreases the incidence of serious long-term outcomes such as cirrhosis or hepatocellular carcinoma. Given these considerations, antiviral treatment should be reserved for patients with chronic hepatitis C who have evidence of liver disease that is compensated.

Dose-modification or discontinuation for hematologic, psychiatric, autoimmune and other adverse events is frequently necessary. Serious adverse events frequently but not always reverse with discontinuation of treatment. Regular clinical and laboratory assessment of patients and patient education are essential to prevent or mitigate serious adverse reactions.

The risk benefit of peginterferon 1.5 μg/kg and ribavirin 800 mg in patients with chronic hepatitis C is acceptable.

The overall risk/benefit of ribavirin doses higher than 800 mg daily with peginterferon 1.5 μg/kg is not known. There is evidence of higher toxicity associated with higher ribavirin dosage without compelling data on known clinical benefits.

Additional studies are needed in the post-marketing phase to explore:

- The optimum dose of ribavirin to determine if a higher doses (administered on basis of body weight) can achieve higher response rates without higher risk of serious irreversibly toxicity.

- The optimum dose of peginterferon to determine if a lower dose (1.0 μg/kg) can achieve a similar response rate without the higher risk associated with the 1.5 μg/kg dose.

- The optimum duration of peginterferon and ribavirin treatment in patients with high likelihood of response such as patients with HCV genotype 2-3, and genotype 1 with low viral load. The aim is to determine if shorter duration of treatment (e.g. 6 months) can achieve similar response rates while avoiding the added toxicity of longer treatment.

- The effects of food on single-dose ribavirin absorption (e.g. effects of high fat vs. high non-fat caloric intake) and achievement of steady state after multiple dosing of ribavirin.

REGULATORY ACTION

Peginterferon alfa-2b and ribavirin has been shown to be safe and effective for the treatment of compensated chronic hepatitis C in patients not previously treated with interferon alpha who are at least 18 years of age. Therefore the marketing application by Schering Plough was approved.